REMARKS

Status of the Claims

Claims 1, 2, 5, 6, and 12-19 are pending in the present application. Claims 4 and 7-11 were previously canceled. Claim 3 is presently canceled. Claims 1 and 5 are amended to specify 'wherein said transgenic non-human mammal, (claim 1), or said part of the transgenic non-human mammal, (claim 5), produces high affinity antibody-producing B cells.' The claims are amended without prejudice or disclaimer. Support for this amendment is found throughout the application as originally filed including, *e.g.*, on page 1 lines 8-10. Applicants respectfully request entry of the instant amendment as well as the amendment submitted to the Office on December 29, 2008. Reconsideration is requested.

Substance of the Interview

Applicants and Applicants' representative thank the Examiner for extending the courtesy of an interview on February 6, 2009. The substance of the interview is essentially reflected in the Interview Summary issued on February 17, 2009. Briefly, the rejections of the present claims under 35 U.S.C. § 103(a) and 35 U.S.C. § 112, first paragraph, enablement, were discussed. An amendment to the independent claims was also discussed. In accordance with this discussion, the claims are amended to specify, 'wherein said transgenic non-human mammal, (claim 1), or said part of the transgenic non-human mammal, (claim 5), produces high affinity antibody-producing B cells." The Examiner indicated that this amendment may overcome the rejection under 35 U.S.C. § 103(a). Applicants further comments in response to the issues discussed under 35 U.S.C. § 112, first paragraph, enablement, are submitted herein below.

Issues Under 35 U.S.C. § 112, First Paragraph, Enablement

Claims 1-3, 5, 6, and 12-19 remain rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The claims remain rejected for the reasons of record as described in the Office Action, which issued on October 11, 2007. The issues discussed in the Office Action of October 11, 2007, were further discussed in the

Examiner interview of February 6, 2009. Specifically, the Examiner stated in the Office Action of October 11, 2007, and the February 6, 2009, interview that a) the transgenic mammal generated from GANP gene-transfected ES cells or its progeny, as described in claim 3, allegedly lacks enablement support in the present application; b) not all animal species use somatic hypermutation as the primary mechanism to generate structurally heterogenous V regions; accordingly, without undue experimentation, an ordinary artisan would know whether or not overexpression of GANP in species other than mice, can result in mutations that occur frequently, such that high affinity antibodies can be detected in other transgenic non-human mammals; c) different lines of mice described in the present application have different mutations in the V_H186.2 region; accordingly, a skilled artisan allegedly would not know, without undue experimentation, which of the mutations are correlated to high affinity binding; d) the specification allegedly fails to support that GANP gene can routinely be overexpressed in the described mammals to obtain high affinity antibodies; e) Figure 29 is allegedly insufficient to demonstrate that GANP transgenic mouse-derived hybridoma clones generate high-affinity antibodies.

a. ES cells

Although Applicants do not agree that the present application fails to support that transgenic mammals may be generated from GANP gene-transfected ES cells or its progeny, claim 3 is canceled to expedite prosecution. Accordingly, this aspect of the enablement rejection is overcome.

b. Somatic hypermutation is the primary mechanism used to generate structurally heterogenous V regions in mammals.

The present application teaches that enhancement of antibody affinity can be achieved by inducing somatic hypermutations in antibody variable region genes. Overexpressed GANP promotes somatic hypermutations *see* page 15, lines 5-9, in the application as originally filed. However, during the interview, the Examiner stated that gene conversion, rather than somatic hypermutation, occurs in some species. In support of this contention, the Examiner referenced Li *et al.*, *Genes and Development*, 18:1-11, *see also* Office Action of October 11, 2007, page 10.

Li *et al.* teach that somatic hypermutation is the prominent mechanism in mice and humans, whereas gene conversion occurs in chickens and some other species, *see* page 1, left column of Li *et al.* Applicants note that the claims submitted on December 29, 2008, in response to the final Office Action are limited to the mammals, bovine, horse, pig, goat, rabbit, dog, cat, mouse, rat, hamster and guinea pig. Applicants submit that an ordinary artisan recognizes that the primary mechanism for generating structurally heterogenous V regions in mammals is *via* somatic hypermutation.

c. An ordinary artisan recognizes that B cells expressing high affinity antibodies are selected during the immune response.

As noted above, the Examiner states that the present application teaches that different lines of mice have different mutations in the V_H186.2 region. Accordingly, the Examiner alleges that an artisan cannot reasonably predict which of the described mutations are correlated to high affinity binding.

The instant invention is based upon Applicants' realization that high affinity antibodies may be generated by using mammals, which overexpress GANP in B cells. During the progression of the immune response, hypersomatic mutations generate a population of antibodies with structurally heterogeneous V regions. Cells expressing antibodies having a mutation that results in high affinity hapten binding, such as W to L at position 33, are preferentially selected. That is, B cells with the highest affinities for antigen will be selected to survive. B cells that have undergone somatic hypermutation, but bind antigen with lower affinity, will be out-competed and will be deleted. By increasing the rate of somatic hypermutation, however, a high affinity antibody-expressing cell may be out-competed by a different, even higher affinity antibody-expressing cell.

Transgenic B cells overexpressing GANP are more likely to generate higher affinity antibodies than those not overexpressing GANP since GANP will increase the rate of somatic hypermutations resulting in a greater probability that a rarer high-affinity binding associated mutation will be produced, and, accordingly, selected. Based upon the foregoing, an ordinary artisan does not know *a priori* which mutations in, *e.g*, the V_H186.2, region, will be selected. Since the GANP transgenic non-human mammal increase the rate of somatic hypermutations,

GANP transgenic non-human mammals can readily produce rarer higher-affinity binding antibodies.

d. An ordinary artisan recognizes from the prior art that transgenes can be expressed in mammals other than mice and predictable phenotypes can be obtained.

During the Examiner interview and in the Office Action of October 11, 2007, the Examiner stated that an ordinary artisan would not have recognized at the time of the invention, that the GANP gene could routinely be overexpressed in non-human mammals, other than mice, to obtain the phenotype described in the instant claims, *i.e.*, production of high affinity antibodies, *see* Office Action, October 11, pages 7-8. In addition, the Examiner stated that there are numerous limitations in using transgenic animals as models of disease, *see* Office Action, page 8.

Applicants submit that undue experimentation is not required to express the transgene described in the instant claims or a transgene of interest in a non-human mammal to obtain a predictable phenotype. Such procedures are routine in the art. For example, Applicants submit Exhibit A. *i.e.*, Maass *et al. Cardiology*, 2000, 15:189-196, which describes animal models of hypertrophic cardiomyopathy. Exhibit A exemplifies that transgenic animals, other than mice, may be used to obtain predictable phenotypes, *see*, *e.g.*, abstract. *See also*, page 190, left column, which states "[i]n the past few years, an increasing number of transgenic animals have been created that model human FHC mutations and disease." *See also*, page 190, left, column paragraph 3, which states "[t]able 3 presents a summary of the transgenic animals further described herein." These animals include mouse, rat, hamster rabbit and cat, *see* Table 3. Accordingly, contrary to the Examiner's assertion, transgenic animal models, other than mice, have been routinely used to obtain predictable phenotypes, such as the animals models of hypertrophic cardiomyopathy, described in the Exhibit. Based upon the foregoing, Applicants believe that this aspect of the rejection is overcome.

e. An ordinary artisan recognizes that the specification adequately teaches how transgenic mammals can be used to produce high affinity antibodies.

During the interview, the Examiner stated that the present application and Figure 29 is insufficient to demonstrate that GANP transgenic mouse-derived hybridoma clones generate high-affinity antibodies. Specifically, the Examiner stated that Figure 29 only shows a single control. The Examiner further stated that if Applicants could provide additional data, which demonstrate that the controls cluster near W2-7 in Figure 29, such controls would support that the instant hybridoma clones produce high affinity antibodies.

Applicants further reiterate that the present application provides adequate guidance, which enables a skilled artisan to recognize that the described transgenic animals produce high affinity antibodies. As is understood by a skilled artisan, increased somatic hypermutations in transgenic animals are associated with affinity maturation of hapten specific B cells and enhanced antibody affinity, *see e.g.*, page 35, lines 1-2 and page 14, lines 28-29 in the originally filed application. As is evident from, *e.g.*, Figure 10 and page 34, lines 28-31, in the present application, GANP expression resulted in an increase in somatic hypermutations in the transgenic mice encompassed by the present claims in comparison to wild-type mice.

In addition, as noted previously, Figure 29 demonstrates that high-affinity antibodies are generated using GANP transgenic mouse-derived hybridoma clones. The affinity of antibodies, generated after immunization with NP-CG antigen, *i.e.*, anti-NP antibody, was evaluated based upon the ability of the antibodies to bind to NP2-BSA, *i.e.*, two NPs coupled to BSA per molecule and NP17-BSA, *i.e.*, seventeen NPs coupled to BSA per molecule. Specifically, in ELISA analysis, the higher the value of NP2/NP17, (*i.e.*, the ability to bind to NP2-BSA/the ability to bind to NP17-BSA), the stronger the strength of binding to NP2-BSA, and, accordingly, the higher the affinity to the NP group. The results in Figure 29 show that the GANP transgenic mouse-derived hybridoma clones have higher affinity to the antigen compared to wild-type mouse-derived hybridoma clones. Applicants further submit that the control value, which describes a hybridoma derived from wild-type mouse, in conjunction with the disclosure in the present application, is sufficient evidence for an ordinary artisan to have recognized that the claimed transgenic mammals, parts thereof and cells thereof produce high affinity antibodies.

Based upon the foregoing, Applicants submit that the present application adequately provides enablement support for the instant claims. Accordingly, withdrawal of the rejection is respectfully requested.

Issues Under 35 U.S.C. § 103(a) Obviousness

Claims 1-3, 5, 6, and 12-19 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over Kuwahara *et al.*, *Blood*, 2000, 95:2321-2328, ("Kuwahara") in view of Jaenisch, *Science*, 1988, 240:1468-1474, ("Jaenisch") in view of Maas *et al.*, *The Journal of Immunology*, 1999, 162:6526-6533, ("Maas") for the reasons of record as described in the Office Action, which issued on October 11, 2007, *see* Advisory Action, page 8.

The Examiner states that Kuwahara discloses that germinal center-associated nuclear protein co-immunoprecipitates with MCM3 in B cells and that GANP is upregulated in differentiated cells and arrests the cell cycle. The Examiner further alleges that Kuwahara posits that "a function of GANP is inactivation of MCM3 by means of binding." (*see* Office Action of October 11, 2007, page 16). The Examiner admits that Kuwahara does not disclose or suggest the *in vivo* role of GANP. However, the Examiner asserts that Jaenisch discloses a common method for generating a transgenic mouse using microinjection technology. Maas is cited for the disclosure of a 6.3 kb genomic fragment with the CD19 promoter, which contains a critical B cell-specific activator protein/pax-5 site, allowing generation of transgenic mice that express the gene of interest in only B cells. According to the Examiner, it would have been obvious to one of ordinary skill in the art to combine these references to achieve the instant invention.

Although Applicants do not agree that the cited references render the instant claims obvious, the claims are amended to expedite prosecution. As amended, claim 1 is directed to a transgenic non-human mammal selected from the group consisting of bovine, horse, pig, goat, rabbit, dog, cat, mouse, rat, hamster, and guinea pig, comprising a transferred recombinant mouse GANP gene or human GANP gene encoding and expressing a protein of SEQ ID NO: 2 or 4 or progeny thereof encoding and expressing said protein, wherein said transgenic non-human mammal produces high affinity antibody-producing B cells. Claim 5 is also amended to

specify "wherein said part of the transgenic non-human mammal produces high affinity antibody-producing B cel."

Applicants submit that none of the cited references, either alone or in combination, teach or suggest a transgenic non-human mammal comprising recombinant mouse GANP gene or human GANP gene expression, *wherein said transgenic non-human mammal, (claim 1), or said part of the transgenic non-human mammal, (claim 5), produces high affinity antibody-producing B cell.* Accordingly, Applicants believe the rejection is overcome and respectfully request withdrawal of the rejection.

CONCLUSION

In view of the above amendment and remarks, applicants believe the pending application is in condition for allowance. Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact L. Parker, Reg. No. 46,046, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

Dated: JUN 29 2009

Respectfully submitted,

By _____
Gerald M. Murphy, Jr.
Registration No.: 28,977
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
P.O. Box 747
Falls Church, Virginia 22040-0747
(703) 205-8000
Attorney for Applicant

GMM/LTP/jg